66. The mutant *ras* peptide-carrier molecule conjugate according to claim 25, wherein the carrier molecule is selected from the group consisting of influenza peptide, tetanus toxoid-CD4 epitope, Pseudomonas exotoxin A and poly-L-lysine.

67. The mutant *ras* peptide-carrier molecule conjugate according to claim 25, wherein the carrier molecule is tetanus toxoid.

68. The pharmaceutical composition according to claim 33, wherein the biological response modifier is interleukin 2.

69. The pharmaceutical composition according to claim 34, wherein the adjuvant is QS21, alum or incomplete Freund's adjuvant.

70. The pharmaceutical composition according to claim 32, further comprising interleukin 2, interleukin 6, interleukin 12, interferon, tumor necrosis factor, GM-CSF, β_2-microglobulin, or combinations thereof.

REMARKS

On September 27, 2000, Applicants' representative orally elected the species:

YLVVVGADGV, not YLVVGADGV as reported by the Examiner in the present Office Action.

The Examiner has stated that claims 16-24 were withdrawn from further consideration under 37 C.F.R. §1.142(b) as being drawn to a non-elected species.

Applicants would urge that should an allowable claim generic to all the claimed species be found allowable, that all the claims to species in excess of one should be allowable if written in dependent form or otherwise written to include all the limitations of the generic claim (37 C.F.R. §1.141(a)). (MPEP 820).

Applicants, in the present Amendment, have amended claim 25 to its original generic form. Claim 66 has been added, corresponding to original claim 26, to recite species of carrier molecules. Claim 67 has been added to recite the specific carrier molecule, tetanus toxoid, the species previously elected by Applicants.

Applicants have amended claim 33 to its original generic form of biological response modifier. Claim 68 has been added to recite the specific species, interleukin 2, the species previously elected by Applicants.

Applicants have amended claim 34 to its original generic form of adjuvant and generic liposome formulation. Claim 69, corresponding to original claim 35 has been added directed to species of adjuvants. Previously elected species, Ribi Detox™, has been cancelled. Applicants now elect incomplete Freund's adjuvant as the species of adjuvant.

Claim 32 has been amended to clarify the subject matter of the invention.

Claim 70 has been added which corresponds with original claim 37.

No new matter has been added by the amendment. Applicants further submit that claims 66-70 are directed to subject matter of previously elected Group I. Entry thereof is respectfully requested.

Attached as Exhibit 1 is a marked-up version of the changes made to claims by the present amendment. The attached page is entitled "Amendment of Claims 10-13, 25, 27 and 32-34 With Markings to Show Changes Made".

35 U.S.C. §112, Second Paragraph Rejections

Claim 10 was rejected as indefinite in the recitation of "elicits peptide-specific human $CD8^+$ cytotoxic T lymphocytes".

In response, Applicants have amended claim 10 to recite, "elicits a peptide-specific human $CD8^+$ cytotoxic T lymphocyte immune response". Claim 27 ahs been similarly amended.

Claim 11 and 12 were rejected for the recitation of "about". Claims 11 and 12 have been amended to delete this recitation.

Claim 34 was rejected for the recitation of the trademark name, "RIBI Detox™". Claim 34 has been amended to recite the generic "adjuvant".

Applicants submit that claims 10, 11, 12 and 34, as amended, particularly point out and distinctly claim the subject matter that Applicants regard as the invention. Reconsideration and withdrawal of the rejections under 35 U.S.C. §112, second paragraph is respectfully requested.

35 U.S.C. §103(a) Rejection

Claims 10-15, 27 and 32 were rejected under 35 U.S. C. §103(a) as being unpatentable over Van Elsas et al (1995) or Gjertsen et al (1996) in view of Ruppert et al or U.S. Patent No. 5,861,372 (1999).

Van Elsas et al is stated by the Examiner to teach a mutant *ras* peptide of about 10 or 13 amino acids in a pharmaceutically acceptable carrier comprising the sequence KLVVVGADGV that the Examiner states binds human MHC HLA-A and "thus would be inherently capable of eliciting $CD8^+$ lymphocytes".

Gjertsen et al is stated by the Examiner as teaching a mutant *ras* peptide of about 10 or 13 amino acids comprising the sequence KLVVVGADGVGKSALTI that binds MHC HLA-A and elicits $CD8^+$ lymphocytes.

The Examiner states that Van Elsas et al and Gjertsen et al differ from the claimed invention in that the peptides taught by the references begin with an N-terminus K while the claimed peptide, K has been replaced by a Y at the mutant ras N-terminus.

Ruppert et al is cited as teaching the addition or replacement of an N-terminus amino acid residue with a Y improves binding of a peptide to HLA-A2.

The '372 patent is cited as teaching that Y can be added to peptide fragments to facilitate the addition of detectable labels to said fragments.

The Examiner concludes that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to replace an N-terminus K, on the mutant *ras* peptide taught by Van Elsas et al or Gjertsen et al with an N-terminus Y, as taught by Ruppert et al or the '372 patent and the motivation would have been to facilitate either better HLA-A2 binding as taught by Ruppert et al or to facilitate labeling as taught by the '372 patent.

Applicants respectfully traverse the rejection. Applicants would first like to point out that a patent used as a prior art reference under §103(a) is only available as of its issue date. In this regard the secondary reference, U.S. Patent No. 5,861,372 is not prior art to the present application, as the issue data of the '372 patent is well after Applicant's filing date and priority dates. Thus, the rejection based on the '372 patent should be withdrawn.

Applicants submit that the present invention are mutant ras peptides comprising a sequence of 10 or more amino acids, in which two or three positions are substituted in comparison to the wild-type *ras* sequence. Neither Van Elsas et al or

Gjertsen et al teach or suggest mutant ras peptides having multiple substitutions at two or three positions. Both teach single substitutions at position 12 (Van Elsas et al) or at position 12 or position 13 (Gjertsen et al). Neither Van Elsas et al or Gjertsen et al teach or suggest substitutions at position 12, position 5 and/or position 7.

The Examiner relies on Ruppert et al as providing the motivation to one skilled in the art to make an N-terminal substitution of Y for K. Applicants submit that the disclosure of Van Elsas et al would lead one skilled in the art away from reliance on Ruppert et al. First, Applicants must point out that Ruppert et al fail to disclose *ras* or a *ras* (mutant or non-mutant) peptide. Second, Van Elsas et al reliance on Ruppert et al lead them away from further studies on *ras* peptides encompassing positions 5 through 14.

Van Elsas et al state at page 390, 2nd column, under Results:

> To identify HLA-A*0201-binding peptides, the protein sequences derived from human N-ras, H-ras, and K-ras genes were screened for the presence of peptide motifs for HLA-A*0201 (Ruppert et al, 1993). Several wild-type and mutant peptides of 9 to 11 amino acids in length were found to carry anchor amino acids at position 2 as well as at the C-terminal end. In addition, several peptides around p21 ras positions 12/13 or 61 containing one anchor residue and carrying a mutation were selected (Table I). Two p21 ras peptides strongly bind to HLA-A*0201 molecules using the MHC peptide binding assay (Table I). The 9-mer peptide (CLLDILDTA) with wild-type sequence and the 11-mer sequence extending to position 61, harboring a Q to L substitution (CLLDILDTAGL) which generated the anchor L (Ruppert et al, 1993) at the carboxy-terminal end of the peptide, did stabilize HLA-A*0201 on T2 cells to roughly the same extent (Fig. 1).

Table 1 in Van Elsas et al clearly shows that all of the eight 10-mer ras peptides 5-14 had virtually no binding to HLA-A*0201, peptides constructed based on the teachings of Ruppert et al. Van Elsas et al also conclude that peptides that do not

bind HLA-A*0201 would be unsuitable for CTL response induction (p. 390, 2nd paragraph, lines 7-4 from the bottom). One must conclude that Van Elsas et al believed the ras peptides 5-14 were unsuitable for CTL response induction as no further studies of these peptides were undertaken. Rather, Van Elsas et al concentrated their efforts on the two peptides that demonstrated strong binding to HLA-A*0201, CLLDILDTA and CLLDILDTAGL.

Van Elsas et al also has data to contradict the Examiner's statement that peptides that bind HLA-A must inherently be capable of eliciting a $CD8^+$ lymphocyte response. Van Elsas et al state at page 394, first column:

> A wild-type p21 ras peptide strongly binding to HLA-A*0201 does not induce CTL.
>
> We have not yet been able to induce responses against the wild-type CLLDILDTA sequence, although the peptide binds to HLA-A*0201 with equal affinity as the 11-mer-mutated peptide.

Gjertsen et al also fails to provide predictability to one skilled in the art in successfully eliciting a peptide-specific human $CD8^+$ T lymphocyte immune response using a mutant *ras* peptide. Gjertsen et al discloses that only 2 of 5 patients demonstrated a T-cell response to immunization with a ras peptide having a single substitution at position 12 (see Table III).

Ruppert et al teach a myriad of combinations of amino acids and positions for substitution of a generic 9-mer and 10-mer peptide that could possibly enhance binding of the generic peptide to HLA-A2. However, even if one skilled in the art would have been motivated to turn to Ruppert et al to make a mutant *ras* peptide, one could not have predicted a likelihood of success in obtaining a mutant *ras* peptide capable of

eliciting a peptide-specific human $CD8^+$ cytotoxic T lymphocyte immune response using those mutant *ras* peptides. The likelihood of success cannot be predicated on the results of Van Elsas et al or Gjertsen et al as discussed above.

Other prior art have shown that reliance on the teachings of Ruppert et al for constructing peptides modeled after the HLA-A2 binding motif does not provide predictability in constructing peptides that bind to HLA-A2 and of those peptides that do bind HLA-A2, Ruppert et al do not provide predictability that the peptides will elicit a peptide-specific human $CD8^+$ cytotoxic T lymphocyte immune response.

Pogue, R.R. et al Proc. Nat'l Acad. Sci Vol. 92, pp. 8166-8170, August 1995, discloses the tests of 10 pol-9 mer peptides (see Table 1) constructed based on the HLA-A*0201 binding motif of Ruppert et al (citation 4) for both binding and pol-specific CTL recognition (Exhibit 2). They report that all the position 3 substitutions resulted in higher affinity peptides which were not recognized by pol-specific CTLs. They further report that almost all of the position 4-8 substitutions displayed decreased binding and little or no recognition by pol-specific CTLs (see page 8169, column 2, 2nd paragraph).

Rivoltini, L. et al J. Immunol. vol 154, No. 5, March 1, 1995, pp. 2257-2265, disclose that of the twelve 9-mer MART-1 peptides (see Table I) selected according to the peptide binding motif of HLA-A2.1 (citing Ruppert et al) (see page 2258, 1st column, 3rd paragraph), only one was able to induce CTL lines with specific recognition for melanoma cells (see page 2261 – Discussion). (Exhibit 3).

As previously discussed, the mutant *ras* peptides of the present invention comprise a sequence of 10 or more amino acids in which two or three positions are

substituted in comparison to the wild-type *ras*. Applicants have found that mutant *ras* peptides comprising multiple substitutions have enhanced capacity to elicit $CD8^+$ T lymphocyte immune responses. A peptide of the present invention with a substitution at position 5 and position 12 (Y5D12), compared to the wild-type *ras* sequence, greatly enhanced cytotoxic T cell activity against antigen-pulsed target cells compared to the wild-type *ras* (K5G12) and enhanced activity compared to the ras peptide having a single substitution (K5D12) (see Figure 12). Such a result could not have been predicted by one skilled in the art based on the combined teachings of Van Elsas et al or Gjertsen et al in view of Ruppert et al, especially in light of Pogue et al 1995 and Rivoltini et al, 1995.

Reconsideration and withdrawal of the rejection of claims 10-15, 27 and 32 is respectfully requested.

35 U.S.C. §103(a) Rejection

Claim 25 was rejected under 35 U.S.C. 103(a) as being unpatentable over Van Elsas et al (1995) or Gjertsen et al (1996) in view of Ruppert et al or U.S. Patent No. 5,861,372 (1999) as applied to claims 10-15, 27 and 32 above, and further in view of U.S. Patent No. 6,039,948 (2000).

The Examiner states that the reference teachings differ from the claimed invention in that they do not teach a mutant *ras* peptide conjugate comprising said peptide and tetanus toxoid. The Examiner cites the '948 patent for a teaching of a tetanus toxoid-pepide conjugate.

The deficiencies of Van Elsas et al (1995), Gjertsen et al (1996) and Ruppert et al have been discussed above by Applicants. U.S. Patent No. 5,861,372

(1999) is not prior art under §103(a) to the present invention. Likewise, Stevens, V.C. U.S. Patent No. 6,039,948, which issued after Applicants' priority dates and is not prior art under §103(a). Should the Examiner cite a parent of 6,039,948, such as U.S. Patent No. 5,006,334 (issued April 9, 1991), Applicants submit that 5,006,334 does not overcome the deficiencies of Van Elsas et al, Gjertsen et al, Ruppert et al and the '372 patent. Stevens has no disclosure of *ras*. Stevens has no teaching or suggestion that would lead one skilled in the art to modify the wild-type *ras* peptide to one having multiple substitutions as claimed by Applicants, let alone make a mutant *ras* peptide conjugated to tetanus toxoid.

Reconsideration and withdrawal of the rejection of claim 25 under §103(a) is respectfully requested.

35 U.S.C. §103(a) Rejection

Claim 33 was rejected under 35 U.S.C §103(a) as being unpatentable over Van Elsas et al (1995), or Gjertsen et al (1996) in view of Ruppert et al or U.S. Patent No. 5,861,372 (1999) as applied to claims 10-15, 27 and 32 above and further in view of U.S. Patent No. 5,800,810 (1998).

The Examiner states that the reference teachings differ from the claimed invention in that they do not teach a mutant *ras* peptide composition further comprising said peptide and interleukin 2. The '810 patent is relied upon for a teaching of a pharmaceutical composition comprising an immunogen and IL-2.

Applicants must point out that U.S. Patent No. 5,800,810 issued on September 1, 1998, after Applicants' priority dates and as such is not prior art under §103(a) to the present invention. Should the Examiner cite an earlier parent of the '810

patent, such as U.S. Patent No. 5,503,841, Applicants argue that the '841 patent does not overcome the deficiencies of Van Elsas et al, Gjertsen et al, Ruppert et al and '372 patent. Doyle et al have no disclosure of *ras* or a mutant *ras*. Thus, Doyle et al would fail to lead one skilled in the art to the mutant *ras* peptides having multiple substitutions as claimed by Applicants.

Reconsideration and withdrawal of the rejection of claim 33 under §103(a) is respectfully requested.

35 U.S.C. §103(a) Rejection

Claim 34 was rejected under 35 U.S.C. §103(a) as being unpatentable over Van Elsas et al (1995) or Gjertsen et al (1996) in view of Ruppert et al or U.S. Patent No. 5,861,372 (1999) as applied to claims 10-15, 27 and 32-33 above and further in view of U.S. Patent No. 6,001,349 (1999).

The Examiner states that the reference teachings differ from the claimed invention in that they do not teach a mutant *ras* peptide composition further comprising said peptide, IL-2 and RIBI Detox™. The '349 patent is cited for a teaching of a pharmaceutical composition comprising an immunogen and the adjuvant, RIBI Detox™.

U.S. Patent No. 6,001,349 issued on December 14, 1999, after Applicants' priority dates and as such the '349 patent is not prior art to the present invention under 35 U.S.C. §103(a).

The deficiencies of the other cited art Van Elsas et al, Gjertsen et al, Ruppert et al, U.S. Patent No. 5,861,372 and 5,800,810 have been discussed by Applicants above.

Reconsideration and withdrawal of the rejection of claim 34 is respectfully requested.

Conclusion

Applicants submit that pending claims 10-25, 27, 32-34 and 66-70 are in order for allowance. Should there by any outstanding matters to address, the Examiner is urged to contact the below-signed agent of record.

Respectfully submitted,

MORGAN & FINNEGAN, L.L.P.

Date: April 11, 2001

By: _____
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EXHIBIT 1

AMENDMENT OF CLAIMS 10-13, 25, 27 AND 32-34
WITH MARKINGS TO SHOW CHANGES MADE

10. (Twice Amended) A mutant ras peptide comprising

Xaa1 Leu Xaa2 Val Val Gly Ala Xaa3 Gly Val (SEQ ID NO:14);

wherein Xaa1 is the amino acid lysine or tyrosine;

wherein Xaa2 is an amino acid;

wherein Xaa3 is selected from the group consisting of aspartic acid, valine, cysteine, alanine, arginine, and serine;

with the proviso that when Xaa2 is valine, Xaa1 is tyrosine

and said peptide elicits a peptide-specific human CD8+ cytotoxic T lymphocyte[s] immune response.

11. (Amended) The mutant ras peptide according to claim 10 wherein the peptide comprises an amino acid sequence of [about] 13 amino acids.

12. (Amended) The mutant ras peptide according to claim 10 wherein the peptide comprises an amino acid sequence of [about] 10 amino acids.

25. (Twice Amended) A mutant ras peptide-carrier molecule conjugate comprising the mutant ras peptide according to claims 10 [1]-23 or 24 and a carrier molecule [comprising tetanus toxoid], said carrier molecule enhances the immunogenicity of the peptide.

27. (Amended) An immunogen for eliciting a mutant ras peptide-specific human $CD8^+$ cytotoxic T lymphocyte[s] immune response comprising a mutant ras peptide according to claims 10 [1]-23 or 24 or combination thereof, said immunogen

elicits a mutant ras peptide-specific human CD8+ cytotoxic T lymphocyte[s] immune response.

32. (Twice Amended) A pharmaceutical composition comprising the mutant ras peptide of claims 10-24 and a pharmaceutically acceptable carrier [comprising tetanus toxoid].

33. (Twice Amended) The pharmaceutical composition according to claim 32, further comprising a biological response modifier [comprising interleukin 2].

34. (Twice Amended) The pharmaceutical composition according to claims 32 or 33, further comprising an adjuvant [comprising RIBI Detox™], a liposome formulation, or an antigen presenting cell.